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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/026,459	02/19/1998	HONG-JI XU	UTXC.506	1781

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EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/026,459	Applicant(s) XU ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,36,37 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34,36,37 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-22-02 has been entered.

2. The amendment filed 6-28-01 has been entered.

3. Amendment to claim 1 has been entered.

4. Claims 1-34, 36, 37 and 44-48 are pending in the instant application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 31-33 and 47-48 remain rejected and newly presented claims 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 3-2-00 and 12-22-00 and as discussed below.

It is noted that claims 47 and 48 have been added to the rejection since they are directed to a pharmaceutical composition comprising a DNA segment of claim 44, which would encompass gene therapy and the claimed invention is not enabled for a method of gene therapy. Accordingly, claims 47 and 48 are rejected to the extent they encompass treatment. It is noted that in addition to the issues raised in the previous office action, another issue is the targeting of the vector or DNA segment to a particular cell in an animal in vivo. It is emphasized that while

progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Deonarain (1998) discussed that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Response to Arguments

Applicant's arguments filed 6-28-01 have been fully considered but they are not persuasive. Applicants' arguments that applicants' specification must be taken as enabling unless there are sufficient reasons to doubt the accuracy of the

disclosure and cannot be questioned on the unsupported skepticism of the examiner are not persuasive. In response applicants attention is drawn to MPEP2164.03, which further discusses In re Marzocchi, the case law cited by the applicants.

"Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]"

In the instant case, the cited prior arts substantiate the doubts that the art of gene therapy is not predictable. As further noted in the MPEP2164.03, "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification."

Additionally, applicants' citing of Ex parte Linn, In re Borkowki et al, and Hybriditech Inc. v. Monoclonal Antibodies Inc are not relevant. Furthermore, gene therapy method is not routine and therefore the In re Wands and In re Jackson are not applicable in the instant case. Furthermore, it is noted that the claims are to methods and not to compositions, and that safety is not an issue in the instant

case, rather the issue is: can an artisan of skill practice the method without undue experimentation in view of the unpredictability of the art of gene therapy and therefore, the case In re Brana is not applicable here. It is noted that applicants arguments are reiterations of those made in their previous response and therefore, all the response presented in the previous office action of 12-22-00 has not be repeated here. Furthermore, applicants have not provided any evidence that the claimed method could be practiced following the guidance present in the specification except for arguing and applicants argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979).

In conclusion, the specification is not enabling for the claimed invention because it does not provide sufficient guidance and working example as to how an artisan of skill would have practiced the claimed invention without undue experimentation and the rejection is maintained for reasons of record set forth in the previous office actions of 12-22-00 and 3-2-00.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 8, 10, 13, 16, 20-30, 34, 36, 37 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fung in view of Dryja et al (EP 259031, 09 March 1988 and Friend et al (Friend et al Proc. Natl. Acad. Sci. 84:9059-9063, 1987) for reasons of record set forth in the previous office action of 12-22-00 and as discussed below.

It is noted that the rejection of claims 47 and 48 is applicable to the extent it reads on a DNA composition and that the rejection is not directed to a pharmaceutical composition.

Response to Arguments

Applicant's arguments filed 6-28-01 have been fully considered but they are not persuasive. Applicants note that the claim requires that there be an insertion, substitution, or deletion in the modified protein and that the modified protein have biological activity at least equivalent to the wild type protein. It is noted that Fung et al clearly states "in one embodiment of the present invention, there is provided an isolated DNA molecule, wherein said molecule is a synthetic mutated functionally active Retinoblastoma protein" see lines 14-18 in column 5)." Furthermore, Fung et al teaches assay methods for assessing the biological activity of the mutant Rb (see example 13). While Fung specifically does not teach to find those mutants which had at least equivalent biological activity as the wild type, an artisan would compared the activity of the mutant proteins to wild type protein to assess if the mutant protein was biologically active or functional. Therefore, Fung teaches methods both for making as well as testing the biological activity of the mutant Rb proteins. Regarding the limitation that the mutation is not in the amino acids 184-192 or 245-262, it is noted that amino acids 5, 230, and 363 would be encompassed by the claimed invention since they are within 378 N terminal amino acids. It is noted that applicants have not provided any evidence as to why the Rb mutants of Fung would not have the biological activity that is at least equivalent to wild type protein. Applicants' arguments, that an obvious to try standard is not a legally sufficient basis to sustain rejection. Again these arguments are not persuasive and it is noted that it is not just obvious to try but also an artisan would have had a reasonable expectation of success in producing the proteins. It is reiterated that applicants have not provided any evidence as to why an artisan would not have been successful in making the claimed proteins. Applicants' argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). Applicants have argued that the protein disclosed in Dryja is explicitly excluded from the claimed subject matter, however, it is noted that applicants did not provide any argument as to how it was excluded when there was 99.9% sequence identity between sequences of Dryja and that of

the instant application and therefore, the protein of Dryja could not be excluded. Additionally, even though Friend does not disclosed activity of the protein, since there is 99.9% sequence identity over the sequence encompassed by the claimed invention, in view of Fung, such activity would be obvious.

9. Claims 3-7, 9, 11, 12, 14, 15, and 17-19 are objected to because they are dependent on rejected claims.

10. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). Applicants are also requested to submit a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER